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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: SAH et al.	Confirmation no.: 8421
Application No.: 09/134,771	Group Art Unit: 1636
Filed: August 12, 1998	Examiner: S. Kaushal
For: HUMAN MESENCEPHALON CELL LINES AND METHODS OF USE THEREFOR	Attorney Docket No.: 10624-009-999

#33

SUBMISSION OF BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
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PO BOX 1450
Alexandria, Virginia 22313-1450

Sir:

In response to the Advisory Action mailed April 14, 2003, Applicants submit herewith an original and two copies of a Brief on Appeal pursuant to 37 C.F.R. § 1.191 and § 1.192.

The fee for the submission of this Brief is believed to be $320.00. Please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this page is enclosed for accounting purposes.

Respectfully submitted,

Attorney for Appellants

Date: July 21, 2003

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Sir:

Pursuant to the provisions of 37 C.F.R. § 1.191 and § 1.192, an appeal is taken herein from the final rejection, dated September 20, 2002, which rejects claims 1-15 and 23-27 of this application. Appellants submit herewith: (a) an original and two copies of this Appeal Brief; and (b) a Petition for Extension of Time of two (2) months, from May 20, 2003 to July 20, 2003 with provision for the required fee.

REAL PARTY IN INTEREST

The real party in interest is the assignee of the above-identified application: Signal Pharmaceuticals, Inc. ("Signal") a company having a place of business at 4550 Towne Center Court, San Diego, California 92121. Signal is a wholly-owned subsidiary of Celgene Corp., a company having a place of business at 7 Powder Horn Drive, Warren, New Jersey 07059.

RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives hereby submit that they are not aware of any appeal or interference that directly affects, will be directly affected by, or will have a bearing on the Board's decision in this appeal.

STATUS OF THE CLAIMS

This application was filed with 24 claims. Claims 16-22 were canceled without prejudice pursuant to a Restriction Requirement (Paper No. 6), filed February 14, 2000). Claims 25 and 26 were added in an Amendment under 37 C.F.R. 1.116 (Paper No. 18), filed March 26, 2001. Claims 11 and 12 were canceled, and claim 27 added, in an Amendment under 37 C.F.R. 1.111 (Paper No. 24), filed June 19, 2002. Accordingly, claims 1-10, 13-15, and 23-27 of this application are under final rejection and are the subject of this appeal. The appealed claims are presented in Exhibit 1 attached hereto.

STATUS OF AMENDMENTS

Subsequent to the September 20, 2002 final Office Action, a Response under 37 C.F.R. § 1.116 was filed on March 20, 2003. In an Advisory Action, mailed April 14, 2003, the Examiner indicated that the Response was entered but did not place the application in condition for allowance for the reasons set forth in the Advisory Action.

SUMMARY OF THE INVENTION

The invention, as recited by the claims on appeal, satisfied the long-felt need in the art for human neural progenitor cell lines whose differentiation is regulatable. Before applicants' invention, researchers had identified human neural stem cells, but their culture and differentiation was difficult, and their use required the repeated use of fresh fetal material that is difficult to obtain. Methods of making immortalized rat neural stem cells were also known, but persons of skill in the art had no success in applying those methods to human neural stem cells. The claimed invention, as first practiced by the Inventors, encompasses a method of conditionally immortalizing human mesencephalon progenitor cells to produce immortalized cell lines, and of differentiating the conditionally-immortalized cells to produce mesencephalon cells. The invention further encompasses the conditionally-immortalized human mesencephalon cells themselves, and the mesencephalon cells differentiated therefrom. These cells have proven highly valuable to researchers interested in treating a wide spectrum of neurological disorders.

ISSUES ON APPEAL

(1) The first issue presented by this appeal is whether the novel method of conditionally immortalizing human mesencephalon stem cells, and differentiating these cells, is obvious under 35 U.S.C. § 103(a) over the combination of *five* references cited by the Examiner, *i.e.*, Hoshimaru *et al.*, *Proc. Natl. Acad. Sci. USA* 93:1518-1523 (1996) and Prasad *et al.*, *In Vitro Cell Devel.* 30A:596-603 (1994) in view of Boss *et al.*, U.S. Patent No.

5,411,883 (1995), Weiss *et al.*, U.S. Patent No. 5,750,376 (1998) and Gallyas *et al.*, *Neurochem. Res.* 22(5):569-575 (1997), even though (1) the combination does not teach all of the limitations of the claims; (2) the combination does not provide a reasonable expectation of success in practicing the claimed methods; and (3) there is no suggestion to combine the cited references.

(2) The second issue presented by this appeal is whether the novel conditionally immortalized human mesencephalon stem cells, and the mesencephalon cells differentiated therefrom, are obvious under 35 U.S.C. § 103(a) over the combination of *five* references cited by the Examiner (*see* (1), *above*) even though conditionally-immortalized human mesencephalon progenitor cells are substantially different biochemical entities from rat cells, and, as a result, there is no suggestion to combine the cited references.

GROUPING OF CLAIMS

Claims 1-5, 9, 10 and 25-27, directed to methods of producing conditionally-immortalized human mesencephalon progenitor cells and the neural cells differentiated therefrom, stand separately from claims 6-8 and 13-15, directed to the conditionally-immortalized mesencephalon progenitor cells and the neural cells differentiated therefrom.

REFERENCES RELIED UPON BY THE EXAMINER

Primary:

Hoshimaru *et al.*, *Proc. Natl. Acad. Sci. USA* 93:1518-1523 (1996) (submitted herewith as Exhibit 2) discloses the production of conditionally-immortalized rat neuronal progenitor cells by transfection with a retroviral vector having a tetracycline-controlled transactivator operably linked to a v-*myc* oncogene. When tetracycline is absent, the oncogene is active, and the rat progenitor cell containing it proliferates but does not differentiate. In the presence of tetracycline, however, the oncogene is inactivated, and the progenitor cell containing it may differentiate into a neural cell.

Prasad *et al.*, *In Vitro Cell Devel.* 30A:596-603 (1994) (submitted herewith as Exhibit 3) discloses immortalized clones of rat nerve cells derived from mesencephalon tissue. Cells from the rat mesencephalon were transfected with plasmids expressing the SV-

40 large T antigen, a transforming protein, plated on a special substrate and in a special selection medium; surviving cells had characteristics of neurons.

Secondary:

Boss *et al.*, U.S. Patent No. 5,411,883 (1995) (submitted herewith as Exhibit 4) discloses a method of preparing neuron progenitor cells comprising obtaining mesencephalon tissue from an embryo, dissociation of the tissue to obtain single cells and cell clusters, culturing any progenitor cells present in a first culture medium that selects for the progenitor cells, and proliferating the progenitor cells in a second medium.

Weiss *et al.*, U.S. Patent No. 5,750,376 (1998) (submitted herewith as Exhibit 5) discloses a method for producing genetically modified neural cells. The reference discloses certain growth factors and growth conditions for culturing neural progenitor cells and neural cells.

Gallyas *et al.*, *Neurochem. Res.* 22(5):569-575 (1997) (submitted herewith as Exhibit 6) discloses the measurement of the concentrations of the neurotransmitters acetylcholine, γ-aminobutyric acid (GABA) and monoamines in immortalized rat or mouse cell lines.

ARGUMENT

The Examiner has failed to make out a *prima facie* case of obviousness against the pending claims. In particular, the Examiner rejects the claims over a combination of several references that (1) does not provide a reasonable expectation of success; (2) does not teach all of the limitations of the claims; and (3) would not be combined by those of skill in the art because there is no suggestion to combine them. In arguing that the combination of references does so, the Examiner has, respectfully, misunderstood the teachings of several of the cited references. Moreover, the Examiner attempts to combine art relating to rat neuronal cells with art relating to human mesencephalic cells, a combination that attempts to combine two different cell types, from the different species, recognized in the art as being substantially different from each other.

At the outset, Applicants address the Examiner's contention that "[Applicants'] arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references," citing *In re Keller*, 642 F.2d 413, 426, 208 U.S.P.Q. 871, 882 (C.C.P.A 1981) and *In re Merck & Co, Inc.*, 800 F.2d 1091,

1097, 231 U.S.P.Q. 375, 380 (Fed. Cir. 1986). The Examiner misconstrues Applicants' arguments. Applicants have consistently argued that there is no motivation to combine the references, and that the *combination* of references does not render the invention obvious. Rather than attacking references individually, applicants have discussed individual references either (1) to show that the reference did not contain any explicit motivation to combine the reference with the remaining cited references, or (2) to demonstrate that the Examiner's interpretation of the reference's teaching was incorrect. Particularly in the case of (2), Applicants must be able to explain what the reference in question actually teaches. As the Board will see, the Examiner is merely using rhetoric to mask the deficiencies of the references.

I. The Method Claims Are Not Obvious over the Cited References

1. The Cited References Do Not Teach Every Limitation of the Claims

The combination of prior art references cited by an Examiner, to render any of the claims obvious, must first teach each and every limitation of those claims. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974); *see also* 2143.03 MANUAL OF PATENT EXAMINING PROCEDURE 2100-128 (2003). Additionally, where an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is also nonobvious. 2143.03 M.P.E.P. at 2100-128. The art cited by the Examiner, however, fails to teach every limitation of the claimed invention. In particular, the cited art fails to teach the use of forskolin and the use of the particular combinations of cytokines claimed in the conditional immortalization and differentiation of human mesencephalon precursor cells, and does not teach the recited monolayer cultures of conditionally-immortalized cells. In arguing that it does, the Examiner has misconstrued the teachings of several of the references. Our reasoning is as follows.

The Examiner cites Hoshimaru *et al.* as teaching the use of forskolin for the differentiation of immortalized neuronal cells into neurons (Advisory Action, at page 3), in a rejection of at least claims 9, 10, and 25-27. The Examiner, however, misconstrues this reference's actual teaching. At page 1522, Hoshimaru states that *previous studies* had found that "several cytokines, or forskolin or growth factors on specific substrates" were needed for differentiation. In contrast, Hoshimaru *et al.* teaches that "suppression of the *v-myc* production is sufficient to differentiate immortalized neuronal progenitor cells into neurons."

(*See* page 1521, right column, heading). A reference must be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448, 230 U.S.P.Q. 416, 419 (Fed. Cir. 1986). Weiss suggests, in passing, the use of forskolin to "influence the differentiation" of precursor cells (see col. 20, lines 46, 51), but does not teach that forskolin may be used to generate *neurons* from the precursor cells. Neither Boss *et al.* nor Prasad *et al.* teach the use of forskolin. Thus, the combination of references cited by the Examiner fails to teach the use of forskolin to cause the differentiation of immortalized neuronal cells into neurons, and cannot be used to reject claims 9, 10 and 25-27 as obvious.

The cited art also does not teach the use of the combinations of cytokines as recited in the claims. In particular, the cited art does not teach the use of GDNF in differentiating the conditionally-immortalized cells, as recited by claims 25-27. In fact, the Examiner nowhere states that the cited art teaches the use of GDNF.

Applicants note that the combination of Hoshimaru *et al.*, Boss *et al.*, and Prasad *et al.* does not teach the combination of EGF, FGF-2 and PDGF in the culture of conditionally-immortalized human mesencephalic progenitor cells, and does not teach the combination of differentiating factors recited in claims 25-27. Thus, these missing teachings must be supplied by Weiss *et al.* for the Examiner's rejection to have even a hint of credibility.

The Examiner cites Weiss *et al.* as teaching "the use of a combination of proliferation inducing growth factors selected from NGF, BDNF, NT-3, NT-4, NT-5, CNTF, FGF-1, FGF-2, EGF, TGFa, TGFb, PDGF, IGFs and interleukins . . . The cited art [*i.e.*, Weiss *et al.*] further teaches in-vitro proliferation of neuronal progenitor cells in the presence of [the] above mentioned growth factors." Advisory Action at page 3 (emphasis in original).

Although not explicitly stated, the Examiner appears to cite Weiss *et al.*, in combination with the remaining cited art, against method claims 1-5, 9, 10 and 25-27. The Examiner both misconstrues the teachings of Weiss *et al.*, and misapplies those teachings to the claims. At col. 17, lines 1-15, cited by the Examiner, Weiss *et al.* suggests that precursor cells be proliferated in EGF and FGF-2. In contrast, Weiss *et al.* suggests that PDGF *influences differentiation* (col. 17, line 12). According to claim 1 of the instant method, differentiation is strictly controlled by the expression of the oncogene. Moreover, Weiss *et al.* teaches that, after culturing in "a proliferation-inducing growth factor," the disclosed stem

cells "begin[] to divide, giving rise to a cluster of undifferentiated cells referred to herein as a 'neurosphere'." (col. 17, lines 17-20). These "neurospheres" are obviously not the monolayer taught by the instant disclosure. Weiss therefore teaches that the combination of EGF and FGF-2 with PDGF has a different *purpose* and achieves a different *result* than in the instant invention. As a result, Weiss *et al.* does not rectify the deficiencies of the remaining cited art, and the combination cannot render the instantly-claimed invention obvious.

Other sections of Weiss *et al.* cited by the Examiner are irrelevant or do not supply the teachings for which the Examiner cites this reference. Col. 22, lines 17-29 teach that various "growth factor products" may be useful in the treatment of CNS disorders. None of the claims of the instant invention are directed to the treatment of CNS disorders. Col. 30, line 17 merely refers to a section heading and provides no useful information. Col. 31, lines 46-64 disclose a list of "biological agents" that may be *tested* to determine their effects on precursor cells (*see* col. 31, lines 29-45). It is clear that the Weiss *et al.* had no idea what the effects of those compounds would be, only that their effects could be tested. Finally, Examples 1-6 teach only the use of EGF in the culture of mouse neural stem cells; Example 7 teaches *differentiation* in EGF-containing medium; and Example 8 teaches the use of CNTF, BDNF or FGF-2 for *differentiation* of the neurospheres. Therefore, Weiss *et al.*, in combination with the remaining cited art, does not teach the culture of conditionally-immortalized human mesencephalon progenitor cells in EGF, FGF-2 and PDGF to produce the cells of the invention, as recited in claim 1.

In sum, Because Hoshimaru *et al.* teaches only the culture in FGF-2 (see page 1519, left column, second full paragraph), Prasad *et* al. teaches only EGF (*see* page 597, right column, first full paragraph, reference 37), Boss *et al.* and Gallyas *et al.* teach *none* of EGF, FGF-2 and PDGF, the combination of these references fails to teach the use of EGF, FGF-2 and PDGF as recited in claim 1 of the instant invention. And since claims 9, 10 and 25-27 depend upon claim 1, the combination of references likewise cannot be used to reject these claims as obvious.

The cited references alone or in combination do not teach the combination of cytokines in the *differentiation* of the conditionally-immortalized human mesencephalon progenitor cells, as recited in claims 25 and 26, respectively, because they fail to teach the use of GDNF. The Examiner concludes that "it would have been further obvious to use a combination of BDNF, CNTF, FGF-2, EGF, PDGF, and IGFs to promote the survival of mesencephalonic dopaminergic neurons in view of Weiss." Advisory Action at page 3

(emphasis in original). Applicants point out that this combination is not claimed. Rather, the Inventors recite the use of a combination of FGF-2, EGF and PDGF in the culture of conditionally-immortalized mesencephalon progenitor cells, and the use of a combination of either forskolin, GDNF and CNTF (claim 26) or forskolin, GDNF, CNTF, IGF-1 and BDNF (claim 27) to differentiate conditionally-immortalized cells *into* neurons. The Examiner's citation of Weiss *et al.* for this point is, therefore, inapt.

Finally, the Examiner, referring to pending claim 1, once again persists in citing Boss *et al.* as teaching "monolayers," in its abstract and at column 11, line 25. Applicants are aware that Boss *et al.* uses the word "monolayer" in the heading of the section that begins at column 11, line 25. However, the Applicants respectfully suggest that the Examiner has ignored *other* statements in Boss *et al.* that indicates that the reference does not actually disclose a "monolayer" as that term is used in the art and in the instant claims. Boss *et al.* specifically states that "[g]ross examination of typical neuron progenitor cell 'monolayer' cultures reveals interconnected three-dimensional structures, rather than the usual two-dimensional monolayer observed with most cell lines."[1] Col. 6, ll. 4-7. Thus, rather than a monolayer of cells, Boss *et al.* actually discloses cells in interconnected *three-dimensional* structures. In contrast, claim 6 of the instant application clearly recites "*adherent* monolayers" - *i.e.,* a two-dimensional layer of cells. The Examiner has still not explained how the clumps of cells disclosed in Boss *et al.* are adherent monolayers. A reference must be cited for what it *fairly* suggests, *In re Burkel*, 592 F.2d 1175, 1179, 201 U.S.P.Q. 67, 70 (C.C.P.A. 1979), and Boss fairly suggests something other than the adherent monolayers recited in claim 1. Boss *et al.* therefore clearly does *not* teach monolayers, as recited in claims 1 and 6, and cannot be combined with Hoshimaru *et al.* and/or Prasad *et al.* to render these claims obvious.

Even if one assumes that the Examiner is correct that Boss *et al.* teaches monolayers of precursor cells, the Examiner still fails to consider this reference in light of Weiss *et al.*, which teaches that the culture conditions disclosed therein produce *clusters* of cells, not monolayers. The Examiner, therefore, fails to consider the combined teachings of the references.

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[1] Indeed, Boss *et al.* here places "monolayer" in quotes to indicate that the cultures are not monolayers as persons of skill in the art recognize them.

In sum, the combination of references cited by the Examiner fails to teach each and every limitation of the claims, as required for a rejection under 35 U.S.C. § 103. The fact that the combination of *five* references cited by the Examiner fails to supply these teachings underscores the non-obviousness of the pending claims. *See, e.g., ATD Corp. v. Lydall, Inc.*, 159 F.3d. 534, 546, 48 U.S.P.Q.2d 1321, 1330 (Fed. Cir. 1998) (invention not obvious over combination of seven references); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986) (invention not obvious over combination of twenty references).

2. The Cited References Do Not Provide a Reasonable Expectation of Success in Practicing the Claimed Invention

The Examiner also fails to establish a reasonable expectation of success in practicing the claimed invention through the combinations of cited art. Our reasoning is as follows.

In order for a combination of references to render a claim obvious, the combination must have provided, at the time of the invention, a reasonable expectation of success in practicing the invention as claimed. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 U.S.P.Q.2d 1022-23 (Fed. Cir. 1991), *cert. denied* 502 U.S. 856 (1991) (holding that to establish obviousness requires the cited references to show that there was, at the time of the invention, a reasonable expectation of success). The Examiner explains that the combination of references would provide a reasonable expectation of success in practicing the claimed invention "because neuronal progenitor cells are easy to transfect, especially in the presence of proliferation enhancing growth factors, which promotes cell survival." Advisory Action, at page 3. This statement, the Examiner's sole basis for a reasonable expectation of success for the majority of the instant claims, is incorrect for several reasons. Contrary to the Examiner's implication, the invention is more than simply transfecting cells; ease of transfection does not mean that a person of skill in the art would have a reasonable expectation of practicing *the invention* as *claimed*, which encompasses the *transfection* of *human* mesencephalon precursor cells, *culture* of the conditionally-immortalized cells, *differentiation* of these cells, and *culturing* of the neurons obtained thereby.

In making this assertion, the Examiner further presumes that rat cells and human cells are equivalent for the purpose of supporting the cited combination of references.

This contention is the Examiner's sole basis for asserting that culture methods useful for rat cells would apply equally well to human cells. However, this contention is incorrect (*see* Section II, below). In fact, human neuronal progenitor cells are expected to respond differently to pharmacologic agonists and antagonists (*see* Sah *et al.*, "Bipotent Progenitor Cell Lines from Human CNS," *Nat. Biotech.* 15(6):574-580 (1997)), and do not proliferate and differentiate in the same manner as rat cells in response to the same culture conditions. Aside from this contention, the Examiner has provided no basis in the cited art—or elsewhere—for the proposition that *human* neuronal progenitor cells would be "easy to transfect," or to culture, or to differentiate.[2] It is apparent, with respect, that the Examiner has come to this belief based on the Inventors' own disclosure, which is improper. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (holding that the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure).

The assertion of obviousness made by the Examiner is, therefore, essentially that it would be obvious to *try* substituting the rat progenitor cells used in Hoshimaru, *et al.* with human progenitor cells. However, "obvious to try" is an improper basis for a §103(a) rejection. *In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680 (Fed. Cir. 1988). Thus, the invention as embodied in the present invention cannot be rendered obvious by the combination of cited references.

3. There is No Motivation to Combine the Cited References

The Examiner has failed to establish that there exists, either within the cited references themselves or in the general knowledge of the art, a motivation to combine the cited art. Our reasoning is as follows.

In order for the combination of references cited by the Examiner to render any claim obvious, there must have been at the time of the invention a motivation to combine the references. *In re Mayne*, 104 F.3d 1339, 1342, 41 U.S.P.Q.2d 1451, 1454 (Fed. Cir. 1997), *In re Jones,* 958 F.2d 347, 351, 21 U.S.P.Q.2d 1941, 1943-44 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). The motivation cannot come from the Applicant's disclosure. *In re Fine*, 837 F.2d at 1075, 5 U.S.P.Q.2d at 1599

[2] The Examiner is called upon to file a Declaration to support the contention that rat neural stem or progenitor cells are equivalent to human neural stem or progenitor cells. Absent this, the rejection is improper.

(obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art).

The Examiner must provide objective evidence and specific factual findings with respect to the motivation to combine the references. *See In re Lee*, 277 F.3d 1338, 1342-44, 61 U.S.P.Q.2d 1430, 1433-34 (Fed. Cir. 2002). Here, however, the Examiner has provided not the required objective evidence or facts, but only conclusory statements. The Examiner's main argument for combining the cited references is that:

> [o]ne would have been motivated to make immortalized human neuronal progenitor cells wherein the expression of [the]v-*myc* oncogene is driven by [a] tetracycline - controlled tr[a]nsactivator because suppression of [the] v-*myc* oncogene in an immortalized progenitor induces the differentiation of the neuronal progenitor cell. Furthermore, immortalized human neuronal progenitor cells are valuable research tools to understand the molecular mechanism[s] that control the development and function of nervous system cells *in vitro*.

Thus, the Examiner fails to point to any motivation stated within the references themselves that would encourage their combination. This statement, therefore, is legally insufficient to support a rejection for obviousness. *See In re Fine*, 837 F.2d at 1075, 5 U.S.P.Q.2d at 1599.

In fact, there is no motivation within the cited references to combine them. Neither Hoshimaru *et al.* nor Prasad *et al.* teach or suggest the immortalization of human mesencephalon cells. Instead, these references teach the conditional immortalization of *rat* cells; in contrast, neither reference teaches that the method disclosed therein may be used to conditionally immortalize human mesencephalic cells. Hoshimaru *et al.* teaches the conditional immortalization of *rat* cells with tetracycline-regulated *v-myc*. The Examiner states that Prasad *et al.* "teaches that mesencephalic cell[s] could be genetically manipulated." With respect, Applicants argue that this is irrelevant to the instant invention. Prasad *et al.* does not teach or suggest that the methods disclosed therein are applicable to human cells. Rather, Prasad *et al.* very specifically teaches only that the two SV40 constructs disclosed therein could conditionally immortalize *rat* cells. Boss *et al.* teaches the production of non-immortalized human mesencephalon progenitor cells, but does not suggest the immortalization, conditional or otherwise, of the cells disclosed therein. Thus, there is no

motivation to combine Hoshimaru *et al.* or Prasad *et al.* with Boss *et al.* (Weiss *et al.* and Gallyas *et al.* do not teach immortalization.)

The Examiner's statement further fails to explain how the general knowledge of the art would motivate such a combination. For example, the Examiner's statement that the expression of the v-*myc* oncogene induces differentiation fails to explain why such activity would motivate one of skill in the art to combine the cited references. The Examiner further fails to consider that the *only* cited references disclosing immortalized neural cells disclose immortalized *rat* cells. Finally, the Examiner's statement that the claimed cells "are valuable research tools" only points out that the claimed cells were *desirable*, not that a person of skill in the art would have been motivated to combine the references, much less to have the legally requisite expectation of success in obtaining them. However, the desire for a particular result is not a motivation to combine two references; there has to be some teaching in the references themselves or in the art that the references can *be* combined. There is none in the cited references.

The Federal Circuit has stated that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or modification to combine prior art references." *In re Lee,* 277 F.2d at 1343, 61 U.S.P.Q.2d at 1433. This is because "[w]hen prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1271, 20 U.S.P.Q.2d 1746, 1751 (Fed. Cir. 1991), *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051, 5 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988) citing *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). The Examiner, with respect, has not applied this requirement "rigorously."

This conclusion is supported, moreover, by the Examiner's failure to take into account the wide variety of methodologies taught by the cited art, as previously pointed out by Applicants in Paper No. 25. A person of skill in the art would not be guided by these various teachings to the practice the methods and cells claimed in the instant application. For example, the cited references differ in their teachings as to the growth factors to use for proliferation and differentiation. For proliferation, Hoshimaru *et al.* discloses the use of only FGF-2. *See* p. 1519, col. 1, ¶ 3. Weiss *et al.* suggests that cells be proliferated in EGF and FGF-2; that PDGF may influence differentiation (col. 17, line 12); and that CNTF, BDNF or

FGF-2 may be used in the differentiation of precursor cells. Prasad *et al.* does not use growth factors. *See* p. 597, col. 2, ¶ 2. Thus, there is no motivation, either within the references or in the art, to combine a reference disclosing the use of several growth factors, a reference disclosing the use of one growth factor, and a reference disclosing the use of *no* growth factors, to arrive at the claimed method.

In another example, Hoshimaru, *et al.* uses DMEM, a minimal medium, and Ham's F-12, a defined medium, with N2 supplement. *See* p. 1519, col. 1, ¶ 3. Prasad, *et al.* uses only the defined medium MCDB-153, which contains different ingredients than DMEM and F-12, followed after one year by F12 medium. *See* p. 597, col. 2, ¶ 2. Furthermore, the culture of the rat cell lines as taught by Prasad, *et al. requires* the use of tissue culture dishes precoated with a specialized substrate, consisting of bovine serum albumen, fibronectin and collagen. *See* p. 597, col. 2, ¶2.

Moreover, while the method of the instant claim 1 recites the selection of a monolayer of precursor cells, the Examiner attempts to combine Boss *et al.*, a reference that (according to the Examiner) teaches the production of monolayers of precursor cells with Weiss *et al.*, which teaches the use of proliferation-inducing growth factors to produce *clusters* of precursor cells. The Examiner fails to explain the motivation for combining these two conflicting teachings; in fact, if the Examiner is correct, these two references *teach away* from each other. Thus, one of skill in the art would not be motivated to combine these references, with the remaining cited art, to arrive at the claimed invention.

The cited art would not be combined to teach the use of forskolin in the differentiation of the conditionally-immortalized human progenitor cells, as the Examiner suggests. Hoshimaru *et al.*, in contrast to the Examiner's characterization teaches that forskolin is *not* necessary for differentiation (*see* Abstract; page 1521, paragraph under heading "Suppression of v-*myc* Production is Sufficient to Differentiate Immortalized Neuronal Progenitor Cells into Neurons"). Weiss *et al.*, in the context of *non*-transfected progenitor cells, suggests (once) the use of forskolin (*see* col. 20, line 51). The remaining cited references do not disclose the use of forskolin. Thus, the *combination* of references teaches away from the use of forskolin when an externally-regulatable oncogene is employed, as in the current invention. Thus, again, there is no motivation to combine the cited references.

The Examiner has not explained, given the disparate teachings of the cited references, how one of ordinary skill in the art would have determined which elements of the Hoshimaru *et al.*, Prasad, *et al.* or Boss *et al.* teachings to retain, and which to alter, for use with human mesencephalic cells. Neither has the Examiner has pointed to any teaching in the art, or knowledge of one of skill in the art, that would enable such a selection. There is, therefore, no motivation within these references to combine them, or, if combined, to lead one of skill in the art to arrive at the claimed invention. *Compare ATD Corp.*, 159 F.3d at 546, 48 U.S.P.Q.2d at 1330 (no motivation to combine seven references in a crowded field).

Thus, because the motivation to combine the references arise from neither the cited art nor the general teachings of the art, it must have come from the Inventors' own disclosure. It is, of course, improper to use an applicant's disclosure to provide the "hindsight" necessary to combine references that would otherwise not be combined. *In re Vaeck*, 947 F.2d at 493, 20 U.S.P.Q.2d at 1442 (teaching or suggestion to make the claimed combination must be found in the prior art, not in the applicants' disclosure); *In re Deuel*, 51 F.3d 1552, 1558, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995). The Examiner cites *In re McLaughlin* in support of the contention that that the Examiner has used no impermissible hindsight to combine the cited references (*see* Paper No. 26, Office Action, mailed September 20, 2002, at page 3). However, given that neither the references nor the art suggests combining the cited references, the Examiner must have used the teachings of the instant specification to combine the cited references. This is improper. *In re Vaeck*, 947 F.2d at 493, 20 U.S.P.Q.2d at 1442; *In re Deuel*, 51 F.3d at 1558, 34 U.S.P.Q.2d at 1215. As such, the references cited by the Examiner should not be combined to reject the instant claims as obvious.

II. The Cell Claims Are Not Obvious over the Cited Art Because Human Cells Are Not Obvious Over Rat Cells

Claims 6-8, 13-15, 23 and 24, directed to conditionally-immortalized cells and neurons differentiated therefrom, are also not obvious over the cited art. In particular, the combination of art disclosing rat neuronal progenitor cells in combination with art disclosing human neuronal progenitor cells does not make the cell claims of the instant application obvious because rat cells are not equivalent to human cells. Our reasoning is as follows.

The Examiner has not made clear what combination of references is being applied to assert the obviousness of the cell claims, but Applicants will assume it is the Hoshimaru *et al.*, Prasad *et al.*, Boss *et al.* and Gallyas *et al.* references. Hoshimaru *et al.*,

Prasad *et al.* and Gallyas *et* al. disclose rat cells. The Examiner, explaining for the first time in the latest Advisory Action the basis for equating rat cells and human cells, states that:

> In [the] instant case mammalian mesencephalon neuron progenitor cells (mouse and human) are considered to have identical characteristics, therefore the genetic modification and culturing of human mesencephalon neuron progenitor [cells] with combination [*sic*] of know[n] growth factors is not an unexpected finding especially in view of [the] cited prior art of record.

(Advisory Action at page 2). This is an extraordinary claim, which the Examiner fails to support with any citation or authority. The Examiner certainly does not explain what the "identical characteristics" are that would lead one of skill in the art to equate rat or mouse and human neuronal progenitor cells. In fact, the art of progenitor cell culture does not treat human and rat progenitor cells as equivalent. For example, it is expected that rodent neural cells will behave differently in response to pharmacologic agonists or antagonists. *See, e.g.*, Sah *et al.*, "Bipotent Progenitor Cell Lines from Human CNS," *Nat. Biotech.* 15(6):574-580 (1997).

Applicants point out that rat cells are compositions of matter that are substantially different from human cells. The two come from a completely different source, have different biochemical markers, and react differently to culture and proliferation conditions. Rat cells are considered substantially different than human cells by those in the art. The Examiner has provided no reference suggesting or teaching what modifications of the rat neuronal cells should be performed to arrive at the claimed human neuronal cells. Moreover, rat cells cannot be used for the same purposes as human cells, For example, one would not transplant rat cells into a human patient for treatment purposes because such cells would be readily rejected by the patient's immune system!

The Examiner states that "it would have been obvious . . . to substitute the immortalized rat neuronal progenitor cells as taught by Hoshimaru *et al.* and Prasad *et al.* with human mesencephalon neuron progenitors (Boss *et al.*)." (Advisory Action, at p. 3). This proposed substitution fails because the resulting cells would not be conditionally-immortalized human mesencephalon cells. The Examiner, moreover, fails to explain why, or in what context, such a substitution may be made. The Examiner's statement also fails to explain how the cell claims of the instant invention are obvious, because the fact that one cell may substitute for another does *not* mean that the second is obvious in light of the first.

Applicants note, too, that the Examiner has not suggested that the cells of Boss *et al.* could be conditionally-immortalized.

Applicants respectfully suggest that the Examiner may have confounded the product disclosed in the references with the process used to make them. For example, the Examiner states that "it would have been obvious . . . to substitute the immortalized rat neuronal progenitor cells as taught by Hoshimaru et al and Prasad et al with human mesencephalon neuron progenitor cells as taught by Boss et al." In essence, the Examiner argues that the method of Hoshimaru makes the claimed conditionally-immortalized progenitor cells, and the resulting differentiated cells, obvious. In making this argument, the Examiner follows essentially the same obviousness analysis disallowed in *In re Deuel,* 51 F.3d at 1559, 34 U.S.P.Q.2d at 1216. (method of obtaining a DNA molecule cannot render obvious the DNA molecule itself). Thus, the general method of making immortalized *rat* neuronal progenitor cells taught in Hoshimaru *et al.* cannot render obvious the claimed conditionally-immortalized human neuronal progenitor cell itself.

Thus, the combination of Hoshimaru *et al.*, Prasad *et al.* and Boss *et al.* references do not render the cell of the instant invention, or of claims 6, 13-15, 23 and 24, obvious.

Finally, the Examiner once again rejects claims 7 and 8 in part over Gallyas *et al.*, because the Examiner believes that the reference teaches the characterization of mouse or rat immortalized neuronal cell lines by measuring the concentration of various neurotransmitters such as GABA and dopamine. Gallyas *et al.* is irrelevant to claim 7 and claim 8 because neither of these claims recites *methods* for identifying GABAergic or dopaminergic neurons. Instead, the claims are directed to conditionally immortalized *cells* that can *differentiate* into neurons that are GABAergic or dopaminergic. Applicants respectfully restate that the Examiner cites Gallyas *et al.* for the wrong proposition; thus the reference cannot be used in combination with any other cited reference to reject claims 7 and 8.

5. The Invention Satisfies a Long-Felt Need

Finally, Applicants point out that they were the first to produce conditionally-immortalized *human* mesencephalic cells, and to differentiate them into mature mesencephalic neural cells. This accomplishment satisfied a long-felt need in the art because they would be "valuable research tools," as the Examiner has stated. *See, e.g.*, Lotharius *et*

al., "Effect of Mutant α-Synuclein on Dopamine Homeostasis in a New Human Mesencephalic Cell Line," *J. Biol. Chem.* 277(41):38884-94 (2002) (submitted herewith as Exhibit 7). However, the primary art cited by the Examiner against the present invention dates to more than *two years* prior to Applicants' filing date; the Hoshimaru *et al.* reference published in February 1996 (reporting work that had been done in 1995), and the Boss *et al.* reference claims priority to an application filed in 1989. In that time, no other parties were able to generate conditionally-immortalized human mesencephalon cells. The Examiner has failed to explain why, if the cited references render the invention obvious, and the claimed cells and methods were so valuable, no other persons of skill in the art were able to develop these cells and methods prior to the Inventors. The clear reason is that the present invention is not, in fact, obvious, and its execution far less straightforward and routine than the Examiner believes it was at the time of filing.

CONCLUSION

Thus, for the reasons enumerated above, Applicants believe that the instantly-claimed invention is not, in fact obvious over the cited art. Applicants therefore respectfully request the Board to overturn the Examiner's determination that the claims are unpatentable as obvious.

Respectfully submitted,

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Attachments